PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BANNERMAN, David G.
WITHERS & ROGERS
Goldings House
2 Hays Lane
London SE1 2HW
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18.10.2004
Applicant's or agent's file reference: KB523PCT/DGB	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/07333	08.07.2003	10.07.2002

Applicant: KARO BIO AB et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office - Gitschiner Str. 103
D-10958 Berlin
Tel. +49 30 25901 - 0
Fax: +49 30 25901 - 840

Authorized Officer

Koster, A

Tel. +49 30 25901-726

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference KB523PCT/DGB	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/07333	International filing date *(day/month/year)* 08.07.2003	Priority date *(day/month/year)* 10.07.2002
International Patent Classification (IPC) or both national classification and IPC C07C235/52		
Applicant KARO BIO AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.02.2004	18.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Rufet, J Telephone No. +49 30 25901-332

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07333

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-55 as originally filed

Claims, Numbers

1-30 filed with telefax on 27.09.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

see separate sheet

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07333

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 10-18 with respect to ind. applicability

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 10-18 with respect to ind. applicability

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-30
Industrial applicability (IA)	Yes:	Claims	1-9,19-30
	No:	Claims	10-18

2. Citations and explanations

see separate sheet

Re Item I

The new set of claims 1-30 filed with telefax dated 27 September 2004 is based on the examples and the claims as originally filed and is therefore acceptable.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 10-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 01 94293 A (2001-12-13)
D2: WO 00 39077 A (2000-07-06)
D3: WO 02 094319 A (2002-11-28)
D4: CHEMICAL ABSTRACTS, vol. 57, no. 7, 1962, abstract no. 8493g

It should be noted that document D3 indicated in the search report as a P-document has not been taken into consideration for the evaluation of novelty and inventive step, because the priority document has been assumed to be valid (see Official Journal EPO, 11/2001, p. 539-542, especially item 13).

1. The documents D1, D2 and D4 refer to structurally very close thyroid hormone receptor ligands, which differ at least from the claimed compounds by the presence of 2 substituents on the phenoxy group instead of 3 for the claimed compounds; see especially D1, example 1 of p. 27 and D2, p. 7, l. 1-16 and claims 20-22.
2. According to the application (see especially page 2, last paragraph) the problem underlying the invention is to provide compounds which are thyroid hormone receptor ligands and useful in the treatment and prevention of diseases associated with thyroid hormone activity.
D2 and D1 are considered to represent equally the closest prior art, since those documents refer to structurally very close thyroid hormone receptor ligands.
In view of the information given in p. 55, l. 12-13 it is credible that the problem as defined above has actually been solved by the technical features of the claimed

compounds.
However in view of the technical information given especially in D2 (see examples and claims 20-22) and D1 (see example 1) the proposed solution to the abovementioned problem is considered to be obvious.
From D2 (see claims 20-22) and D1 (example 1) the skilled person already knows that 4-hydroxyphenoxybenzamide derivatives or 4-hydroxyphenoxy phenyl acetamide derivatives having one substituent (isopropyl) in ortho position of the 4-hydroxyphenoxy group are thyroid hormone receptor ligands useful in the treatment and prevention of diseases associated with thyroid hormone activity.
The skilled person also knows from D1-D2 (see especially claim 1, the definition of R2, R3) that hydrogen atom, halogen atom and C1-C4 alkyl groups are equivalent substituents for a phenyl ring. He would have therefore, with expectation of success, considered the replacement of the hydrogen atom in ortho position of the 4-hydroxyphenoxy moiety by a C1-C4 alkyl group or a halogen atom as an alternative, if he wanted to produce further thyroid hormone receptor ligands. It is pointed out that such derivations belong to the common practice within the field of chemistry. In absence of truly comparative data showing an unexpected effect of the claimed compounds over the closest compounds of the prior art D1-D2 an inventive step for the claimed subject-matter cannot be acknowledged.

CLAIMS:

1. N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine (E1);
N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E2);
N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E3);
N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E4);
N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E5);
N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E6).
N-[3,5-Dichloro-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E7).
L-N-[3,5-Dibromo-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] valine (E10)
D-N-[3,5-Dibromo-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)phenylacetyl] phenylglycine (E11)
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenylacetyl] valine (E12)
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)phenyl-acetyl]phenylglycine (E13)
L-N-[3,5-Dibromo-4-(3,5-dimethyl-4-hydroxyphenoxy)phenylacetyl]-phenylglycine (E14)
N-[3,5-Dibromo-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E8).
N-[3,5-Dimethyl-2-methyl-4-(3-methyl-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E9).

2. A compound according to claim 1 for use in medical therapy.

3. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a pharmaceutically effective salt thereof, together with a pharmaceutically acceptable carrier.

4. A process for making a pharmaceutical composition comprising combining a compound according to claim 1 and a pharmaceutically acceptable carrier.

5. A pharmaceutical composition comprising a compound according to claim 1 and at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents, growth promoting agents, anti-inflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive agents, cardiac glycosides, cholesterol/lipid lowering agents, appetite supressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.

6. The pharmaceutical composition of claim 5 wherein said additional therapeutic agent is an antidiabetic agent selected from the group consisting of a biguanide, a glucosidase inhibitor, a meglitinide, a sulfonylurea, a thiazolidinedione, a PPAR-alpha agonist, a PPAR-gamma agonist, a PPAR alpha/gamma dual agonist, an SGLT2 inhibitor, a glycogen phosphorylase inhibitor, an aP2 inhibitor, a glucagon-like peptide-1 (GLP-1), a dipeptidyl peptidase IV inhibitor and insulin.

7. The pharmaceutical composition of claim5 wherein said additional therapeutic agent is an antidiabetic agent selected from the group consisting of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, troglitazone, pioglitazone, englitazone, darglitazone, rosiglitazone and insulin.

8. The pharmaceutical composition of claim5 wherein said additional therapeutic agent is an anti-obesity agent is selected from the group consisting of an aP2

inhibitor, a PPAR gamma antagonist, a PPAR delta agonist, a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin reuptake inhibitor, a cannabinoid-1 receptor antagonist and an anorectic agent.

9. The pharmaceutical composition of claim 5 wherein said additional therapeutic agent is a hypolipidemic agent selected from the group consisting of a thiazolidinedione, an MTP inhibitor, a squalene synthetase inhibitor, an HMG CoA reductase inhibitor, a fibric acid derivative, an ACAT inhibitor, a cholesterol absorption inhibitor, an ileal Na^+/bile cotransporter inhibitor, a bile acid sequestrant and a nicotinic acid or a derivative thereof.

10. A method for preventing, inhibiting or treating a disease which is dependent on the expression of a T_3 regulated gene or associated with metabolic dysfunction, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in claim 1.

11. A method for treating or delaying the progression or onset of obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, subclinical hyperthyroidism, non-toxic goiter, thyroid cancer, reduced bone mass, density or growth, eating disorders, reduced cognitive function, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure or a skin disorder or disease, which comprises administering to mammalian patient in need of treatment a therapeutically effective amount of a compound as defined in claim 1.

12. The method as defined in claim 10 wherein the said disease is obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure, or skin disorders.

13. The method according to claim 11 wherein the skin disorder or disease is dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichtyosis, acne, psoriasis,

Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.

14. The method according to claim 10 further comprising administering, concurrently or sequentially, a therapeutically effective amount of at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents, growth promoting agents, anti-inflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive agents, cardiac glycosides, cholesterol/lipid lowering agents, appetite supressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.

15. A method of treating or delaying the progression or onset of a skin disorder or disease which comprises administering to a mammalian patient a therapeutically effective amount of a compound as defined in claim 1 in combination with a retinoid or a vitamin D analog.

16. A method for treating or delaying the progression or onset of obesity which comprises administering to mammalian patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

17. A method according to claim 16 further comprising administering, concurrently or sequentially, a therapeutically effective amount of at least one additional therapeutic agent selected from the group consisting of an anti-obesity agent and an appetite suppressant.

18. A method according to claim 17 wherein said anti-obesity agent is selected from the group consisting of aP2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, cannabinoid-1 receptor antagonists, other thyroid receptor agents and anorectic agents.

19. The use of a compound according to claim 1 in the preparation of a medicament to inhibit or treat a disease which is dependent on the expression of a T_3 regulated gene or associated with metabolic dysfunction.

20. The use according to claim 19, wherein said disease is selected from obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, subclinical hyperthyroidism, non-toxic goiter, thyroid cancer, reduced bone mass density or growth, eating disorders, reduced cognitive function, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure or a skin disorder or disease.

21. The use according to claim20, wherein the skin disorder or disease is selected from dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichtyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.

22. Use according to claim 19 in combination with at least one additional therapeutic agent selected from the group consisting of other compounds of formula I, anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents, growth promoting agents, anti-inflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive agents, cardiac glycosides, cholesterol/lipid lowering agents, appetite supressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.

23. Use according to claim19 in combination with a retinoid or a vitamin D analog wherein said disease is a skin disorder or disease.

24. Use according to claim19 wherein said disease is obesity.

25. Use according to claim 24 in combination with at least one additional therapeutic agent selected from the group consisting of an anti-obesity agent and an appetite suppressant.

26. Use according to claim 25 wherein said anti-obesity agent is selected from the group consisting of aP2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, cannabinoid-1 receptor antagonists, other thyroid receptor agents and anorectic agents.

30. A pharmaceutical composition which functions as a selective agonist of the thyroid hormone receptor comprising a compound as defined in claim 1.